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False Positive Images in the Follow-Up of Patients With Brain Tumors

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In recent years, major advances in the diagnosis and treatment of patients with brain tumors have been seen. Today, evaluation of the central nervous system almost always includes magnetic resonance imaging (MRI). The appearance of a new lesion on the MRI scan of a patient previously treated for a central nervous system (CNS) tumor raises concern for recurrent disease with the need for selection of new, potentially toxic therapy. However, the sensitivity of MRI may allow demonstration of new lesions which are not due to tumor. We now report three patients with medulloblastoma who demonstrated new enhancing lesions on MRI following treatment of their tumors with surgery (3 patients), chemotherapy (2 patients), and radiotherapy (2 patients). Two patients underwent resection of the lesion revealing gliosis. One patient had serial imaging that showed disappearance of the lesions.

This suggests that not all new enhancing lesions in previously treated brain tumor patients represent tumor. Histologic proof of a suspicious lesion should be demonstrated prior to initiation of new therapy. **Med. Pediatr. Oncol. 28: 127–131**

Key words: brain neoplasm; medulloblastoma; MRI

INTRODUCTION

Magnetic resonance imaging (MRI) is becoming the method of choice for the radiographic evaluation of children and adults with brain tumors [1–3]. This technique has several advantages over computed tomography (CT), including superior resolution, multiplanar capability, and freedom from cortical bone artefacts which are particularly troublesome in the posterior fossa [3–7]. MRI with gadolinium-DTPA (Gd-DTPA) enhancement more precisely identifies tumor margin and better delineates tumor from surrounding edema [4,6,7]. Although the difficulty of differentiating postoperative surgical enhancement from residual tumors is well-described, the recognition that postsurgical enhancement appears 48 to 72 hours postsurgery and subsides over several months has led many centers to obtaining baseline MRIs within 48 hours of surgery [8–10]. Newly enhancing lesions appearing several months after surgery are thus felt to represent recurrent disease. We now report three patients with medulloblastoma who developed new enhancing lesions, following treatment, which were strongly suspicious of recurrent tumor but found to be non-neoplastic in origin.

PATIENTS AND METHODS

All three patients were seen at Duke University Medical Center. One patient was initially seen at diagnosis, one after surgery and one patient at "recurrence." Magnetic resonance images were performed in a 1.5-T superconduction magnet (Sigma; General Electric Medical Systems, Milwaukee, WI). T1-weighted images with and without Gd-DTPA enhancement in axial, coronal and sagittal projections as well as T2-weighted axial images were obtained. The T1-weighted images were obtained with a repetition time (TR) of 600 msec and an echo time (TE) of 20 msec (TR/TE = 600/20). T2-weighted images were obtained with a TR of 2200 msec and TE of 30 and 90 msec. The dose of Gd-DTPA (gadopentate dimeglumine, Magnevix, Berlix, NJ) was 0.1 mmol/kg.

SUMMARY OF CASES

Patient 1

A white male was diagnosed at the age of 23.5 years with a left cerebellar medulloblastoma. He underwent a gross total resection of that lesion followed by craniospinal irradiation. Three months following the end of the radiation treatment, five months postdiagnosis, a new nodular enhancing lesion appeared in the midline posterior vermis adjacent to the surgical cavity (Fig. 1A and B). Lumbar CSF was obtained and was negative for tumor cells. This nodular enhancement was highly suspicious for recurrent tumor and the patient was started on monthly chemotherapy consisting of cyclophosphamide at 2 g/m^2/day for 2 days. Follow-up imaging after two cycles

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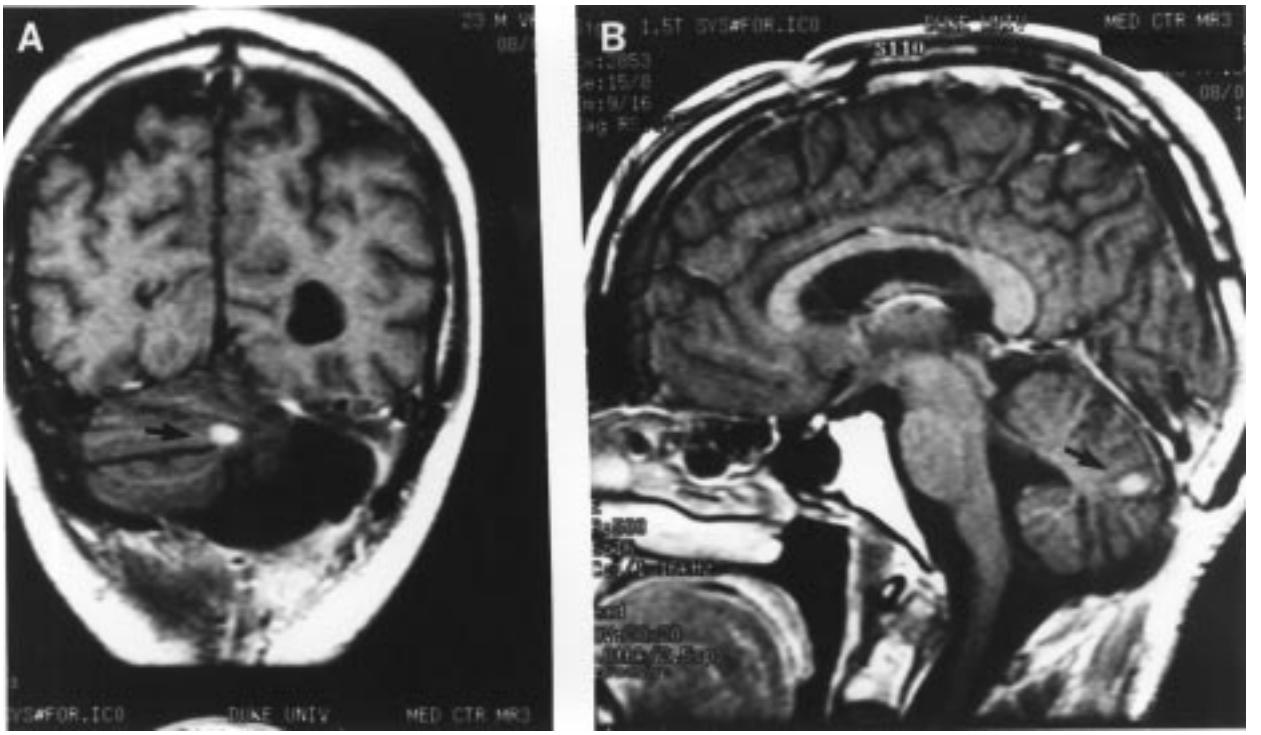

Fig. 1. **A:** T1-weighted coronal postcontrast MR image shows nodular region of contrast enhancement in the midline posterior vermis adjacent to the postsurgical cavity. Arrow points to nodular region of contrast enhancement. Smooth contrast enhancement lines the postsurgical cavity laterally consistent with postsurgical enhancement or scar tissue. **B:** T1-weighted sagittal postcontrast MR image shows similar finding in the midline posterior vermis. This focus of nodular enhancement is highly suspicious for a focus of tumor recurrence or new focus of leptomeningeal dissemination.

showed an unchanged lesion. A positron emission tomography (PET) scan at that time revealed a hypometabolic focus corresponding with the enhancing lesion. The patient underwent resection of the lesion, confirmed on immediate postop MRI, with histologic review showing cerebellum with neuronal loss, gliosis, and necrosis, consistent with radiation effect. No tumor was seen. This "recurrent" lesion was in fact radiation necrosis and no other therapy was offered. The patient has been doing well and his most recent MRI is now 2 years postinitial identification of the suspicious lesion with no new abnormalities noted.

Patient 2

A white female presented at the age of 7 years with headache, vomiting and diplopia. An MRI of her brain confirmed the presence of a cerebellar mass with extension into the spinal canal. She underwent a total gross resection of a medulloblastoma. She was registered on POG #9031 and randomized to receive radiation therapy followed by chemotherapy consisting of cisplatin at 90 mg/m^2/day $\times$ 1 day plus VP-16 at 150 mg/m^2/day $\times$ 2 days for 3 monthly courses followed by 8 monthly courses of cyclophosphamide at 1 g/m^2/day $\times$ 2 days plus vincristine at 2.0 mg/m^2/day $\times$ 1day. Multiple infections complicated her postradiotherapy period and delayed chemotherapy which was ultimately completed. MRI scans were done 1 and 2 months post-therapy, revealing a stable appearance of enhancing trigeminal nerves and interval improvement of a lesion in the left side of the quadrigeminal plate. A repeat scan seven months post-therapy, 21 months postdiagnosis, revealed discrete nodular areas of enhancement involving the posterior left lateral aspect of the medulla and the posterior temporal occipital regions. Three months later, a repeat scan was obtained, revealing progression of the occipital lobe lesions. The lesion in the medulla was not seen. The patient was referred to Duke University Medical Center for further therapy. An MRI obtained at Duke, 2 months from the previous MRI, showed improvement in the bilateral occipital lobe enhancement with still no lesion in the medulla (Fig. 2A and B). An MRI of the spine was negative and CSF cytology was negative for tumor cells. No further therapy was instituted, The patient remains stable neurologically 17 months postinitial identification of the suspicious lesions.

Patient 3

A white female presented at the age of 8 months with persistent head bobbing and failure to attain motor mile-

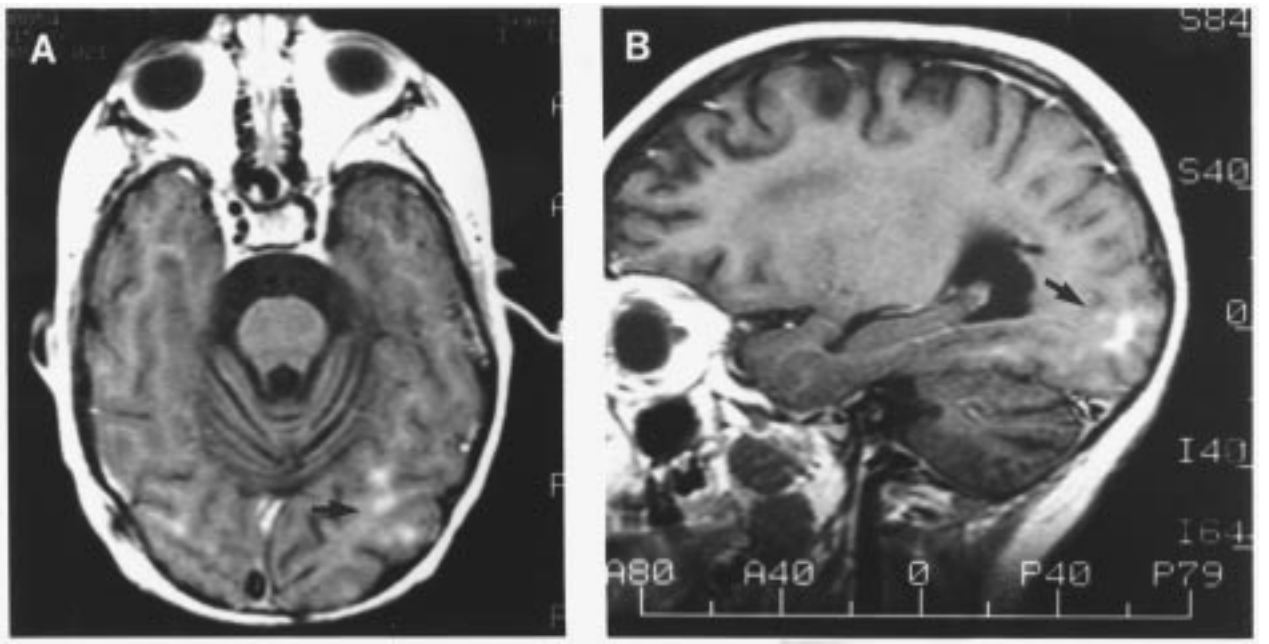

Fig. 2. **A:** T1-weighted axial postcontrast MR image shows abnormal punctate enhancement involving the occipital lobes bilaterally. **B:** T1-weighted sagittal postcontrast MR image shows similar finding in the right occipital lobe. Findings are suspicious for leptomeningeal dissemination of tumor.

stones. An MRI of the head revealed a posterior fossa tumor. She underwent a subtotal resection of a medulloblastoma and was referred to Duke University Medical Center for further therapy. The patient was treated with chemotherapy consisting of cyclophosphamide at 25 mg/kg/week × 4 rotating monthly with cisplatin at 3.0 mg/kg/day for a period of 60 weeks, followed 6 weeks later by an autologous bone marrow transplant using melphalan and cyclophosphamide. Interval and immediate post-therapy scans were all negative. The patient did well until 8 months post-therapy, 26 months postdiagnosis, when surveillance MRI revealed a new area of nodular enhancement in the right cerebellum consistent with tumor (Fig. 3A and B). Myelography with Ct imaging revealed no evidence of metastatic disease and CSF cytology was negative for tumor cells. The lesion was biopsied with histological confirmation of gliosis and no further treatment was given. The patient was subsequently monitored with surveillance negative MRIs obtained at 2-month intervals until November 1994, 30 months following demonstration of gliosis, when a discrete enhancing lesion was noted in a new, different site, the vermis. CSF was still negative and resection of this lesion was undertaken, with histopathology confirming recurrent medulloblastoma. A new treatment has since been initiated.

DISCUSSION

Management of pediatric brain tumor patients has evolved rapidly in the last several years. The use of MRI, particularly since the introduction of Gd-DTPA, has dramatically improved the radiographic evaluation of brain tumors, particularly those located in the posterior fossa [1–7]. The conventional management of a new enhancing lesion in a patient previously diagnosed and treated for a brain tumor is selection of alternative therapy for presumptive recurrent disease. Therapy options for patients with recurrent brain tumors usually consist of phase II studies designed to evaluate new chemotherapeutic or radiotherapeutic interventions. The toxicity of these interventions may be profound if not life-threatening, and selection of this therapy must be based on conviction that recurrent tumor is present. However, radiation necrosis, gliosis and nonspecific inflammatory and vascular changes have been shown to present as new enhancing lesions with histologic review of resected material confirming the absence of malignancy [11–17].

Our three patients ranged in age at diagnosis between 8 months and 23.5 years. They were diagnosed with a medulloblastoma and underwent surgical resection as their first treatment modality. Patient 1 received craniospinal irradiation, patient 2 received craniospinal irradiation followed by chemotherapy, and patient 3 received chemotherapy alone. All had negative MRIs at the completion of their therapy. New enhancing lesions in the primary site and beyond, suspicious of recurrent tumor, were found at 5 months, 21 months and 26 months, respectively, from initial surgery, corresponding to 3 months, 7 months and 8 months following completions of therapy. In two cases,

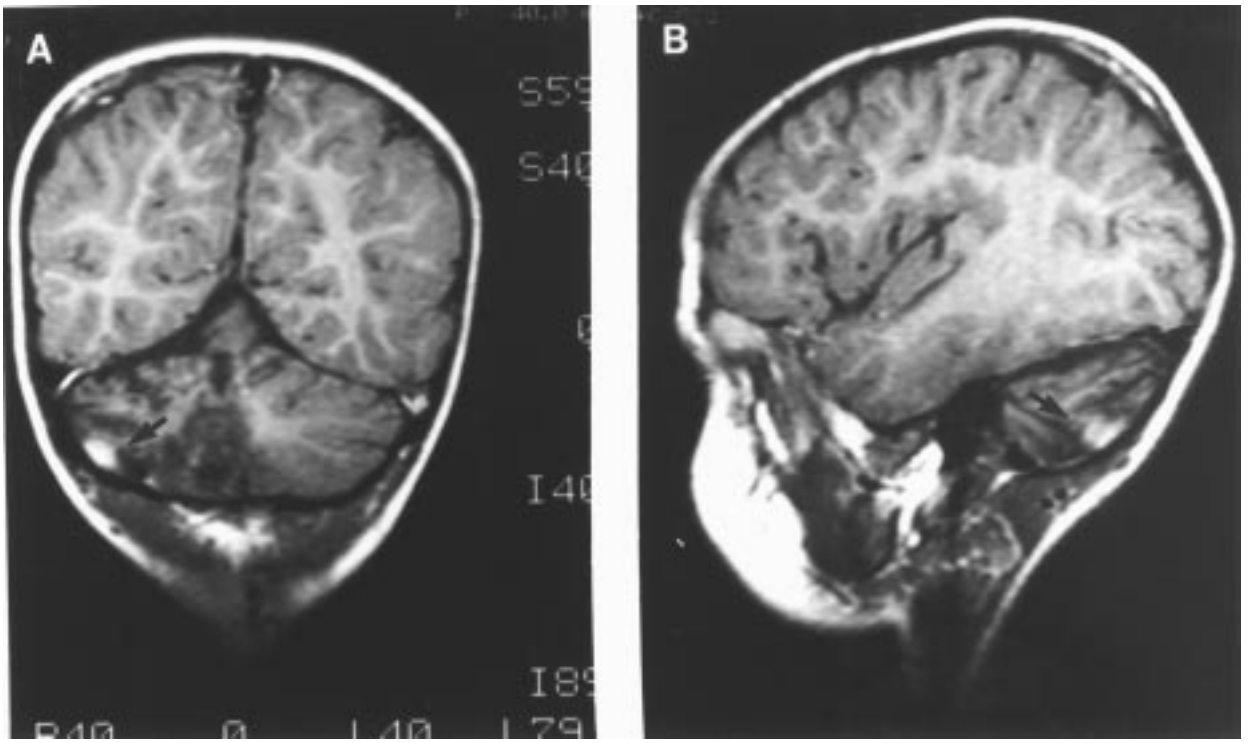

Fig. 3. **A:** T1-weighted coronal postcontrast MR image shows nodular region of contrast enhancement superficial to the right cerebellar hemisphere in the postsurgical region. **B:** T1-weighted sagittal postcontrast MR image shows similar finding superficial and posterior to the right cerebellar hemisphere. Findings are suspicious for a nodular focus of tumor recurrence or leptomeningeal dissemination.

the lesions were resected and found to be consistent with gliosis. Resection was undertaken because of the potentially high toxicity of additional adjunctive therapy. Patient 1 received two cycles of high dose chemotherapy without changes in the lesion and further treatment was to include higher dose chemotherapy with autologous bone marrow transplantation. Patient 3 was 3 years of age at the time the new lesion was identified and therapy would have consisted of craniospinal irradiation known to produce profound neuropsychological, endocrinological and muscular skeletal consequences when administered to young children. In patient 2, follow-up imaging done when the patient was first seen at our institution revealed a decrease in the enhancing lesions. These were assumed to be secondary to radiation and no biopsy was undertaken. At the time of this writing, the patients have been followed for a period of 29 months, 26 months and 42 months, respectively, since diagnosis, 24 months, 17 months and 24 months since the identification of the new enhancing lesions. Two patients remain disease-free with stable neurological function while the third patient (patient 3) demonstrated histologically proven recurrent tumor 24 months later.

Many current phase II protocols for recurrent brain tumors in pediatric patients require biopsy of new enhancing lesions only if they appear 2–2.5 years or more after diagnosis. New lesions within this time of presentation are frequently considered recurrent disease and the patients are eligible for study without histologic confirmation of tumor. Our patients had new lesions appearing at 5, 21 and 26 months postdiagnosis and would have been considered eligible for such therapy. We stress the need to be suspicious that a new enhancing lesion may not always represent recurrent disease and suggest that histologic proof of recurrence be demonstrated prior to initiation of new therapy, unless other evidence of disease, such as demonstration of spinal metastases or positive CSF cytopathology are noted.

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